REMARKS

Claims 49-52, 54-65, and 68 are pending. Claims 1-48 have been cancelled without predjudice or disclaimer. Each of the rejections is addressed below.

Claim Objections

The objection to claims 58 and 59 is overcome by the present amendment.

Rejection under 35 U.S.C. § 103(a)

The Office rejects claims 49, 52, 54-65, and 68, which are directed to methods for inducing new blood vessel growth in myocardial tissue and improving cardiac function, under 35 U.S.C. § 103(a) as obvious over International Publication No. Isner et al., WO 97/14307 (hereinafter "Isner") in view of Hammond et al., U.S. Patent No. 5,880,090, (hereinafter "Hammond"), and U.S. Patent No. Dillman et al., 6,605,274 (hereinafter "Dillman"). For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

Isner

The Examiner acknowledges that differences exist between the prior art and the claimed invention. In particular, the Examiner finds that Applicants' claimed invention differs from that of Isner because (i) Isner fails to teach methods for administering a combination of a nucleic acid encoding an angiogenic protein and at least one angiogenic factor; and (ii) Isner further fails to teach methods for monitoring a cardiac function. At page 6, first paragraph, of the Office Action mailed on February 13, 2007, the Examiner states, "Isner does not teach that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells. Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches . . ." Accordingly, the Examiner has found that Isner alone is not sufficient to make the claimed invention obvious.

Dillmann

To remedy the alleged deficiencies of Isner, the Examiner cites Dillmann and Hammond. Dillmann provides a general description of methods for monitoring cardiac function. Dillmann

fails to teach or suggest methods for administering a combination of a nucleic acid encoding an angiogenic protein and at least one angiogenic factor and subsequently monitoring a cardiac function. Dillmann fails entirely to teach or suggest modifying the methods described by Isner to arrive at Applicants' claimed invention. Such a teaching or suggestion is required in order to establish a prima facie case of obviousness. *In re Dembiczak*, 175 F.3d 994, 50 USPQ 2d 1614 (Fed. Circ. 1999). The Federal Circuit requires the Examiner to show some motivation to combine the references that establish obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). It is not sufficient to show that Applicants' claimed combination *could* be made. Rather, the Examiner must show some particular teaching or suggestion within the references themselves that the combination *should* be made.

Hammond

The Examiner relies on Hammond to remedy the deficiencies of Dillmann and the alleged deficiencies of Isner. Hammond describes methods for increasing **endothelialization** within a synthetic graft using cytokines. Hammond, like Dillman, fails to teach or suggest administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into myocardial tissue; administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, **inducing new blood vessel** growth in a myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal; and **monitoring a cardiac function** by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), fractional shortening (FS), wall motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP).

Hammond merely describes methods to increase the number of endothelial cells that **attach to and coat the surface of a synthetic graft** (column 1, line 60, to column 2, line 5). In contrast, Applicants claims are directed to **inducing new blood vessel growth** in the myocardial tissue of a mammal. Induction of blood vessel growth is a multifaceted biological process that is clearly different from methods Hammond describes for coating a graft surface (column 2, lines 64-67.) One skilled in the art would lack the requisite expectation of success to employ cytokines that increase endothelialization in a synthetic graft as described by Hammond to induce the growth of new blood vessels as recited in Applicants' claims. The Examiner, citing

Hammond, column 3, lines 28-37, alleges that Hammond describes the use of $CD34^+$ cells for the repair of ischemic tissue . Applicants respectfully disagree. In the cited passage, Hammond states that $CD34^+$ cell populations derived from peripheral blood "include a subset of cells that are capable in culture of differentiating into endothelial-like cells." (Hammond, column 3, lines 28-37). Hammond further states that it was "**proposed** that these circulating $CD34^+$ or $Flk\text{-}1^+$ cells participate in the repair of ischemic tissue." The cited passage fails to teach or suggest employing an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby **inducing the new blood vessel** growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal; and **monitoring a cardiac function.**

Asahara

The Examiner rejects claims 50, 51, and 57 under 35 U.S.C. § 103(a) over Isner, Hammond, Dillman and Asahara et al., (EMBO J. 18:3964-3972, 1999; hereinafter "Asahara"). Asahara teaches that "VEGF-induced mobilization of bone marrow-derived EPCs resulted in increased differentiated EPCs *in vitro* and augmented corneal neovascularization *in vivo*." Asahara describes the use of VEGF to induce the mobilization of bone marrow-derived EPCs. Asahara failed to appreciate, as Applicants' did, that the **combination** of a nucleic acid encoding at least one angiogenic protein and at least one angiogenic factor, enhances the induction of blood vessel growth in a myocardial tissue. Asahara plainly teaches that VEGF is sufficient to induce vasculogenesis. To the extent that Asahara directs the skilled artisan towards the use of VEGF to induce vasculogenesis, he teaches away from Applicants' claimed invention, which recites administering to a mammal an effective amount of VEGF **and** a nucleic acid encoding at least one angiogenic protein. Thus, Asahara also fails to teach or suggest Applicants' claimed invention.

In sum, none of the cited references, alone or in any combination teaches or suggests a method for inducing new blood vessel growth in a myocardial tissue of a mammal by administering an effective amount of a nucleic acid encoding at least one angiogenic protein, administering an effective amount of at least one angiogenic factor, and monitoring a cardiac function as recited in Applicants' claims. Applicants were the first to appreciate that blood

vessel growth could be induced using such methods, and that the growth of such blood vessels would improve cardiac function. It is not sufficient that one **could** have made the combination, the cited references must suggest the desirability of making the claimed combination and must further indicate that **the combination if made would have succeeded**. None of the references cited by the Office, alone or in any combination, teaches or suggests Applicants' claimed invention. The Office has failed to establish a *prima facie* case of obviousness. Thus, the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

Double Patenting

Applicants acknowledge that claims 49-52, 54-65, and 68 are provisionally rejected over copending U.S. application No. 10/714,574. With regard to the provisional double patenting rejection over copending application No. 10/714,574, Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double-patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. § 822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.